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(54) Title: PHARMACEUTICAL FORMULATION

(57) Abstract

Pharmaceutical formulations for oral administration, comprising an antibiotic and a β-lactamase inhibitor in the form of a core which comprises a β-lactam antibiotic and a β-lactamase inhibitor, and a surrounding layer around the core.

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Pharmaceutical F rmulation.

This invention relates to pharmaceutical formulations for oral administration, comprising an antibiotic and a β-lactamase inhibitor.

Oral formulations of this type are known, but generally need to be administered three times daily. It is desirable to produce such a formulation in a delayed or sustained release form which may be suitable for less frequent administration. A particularly effective β-lactamase inhibitor is the known compound clavulanic acid and its derivatives (hereinafter collectively termed "clavulanate" unless otherwise specifically identified), especially the potassium salt of clavulanic acid, but clavulanate is very sensitive to moisture. It is therefore desirable to provide clavulanate in an oral formulation in which the clavulanate has improved resistance to environmental moisture.

The invention therefore provides a pharmaceutical granule, comprising a core which comprises a β-lactam antibiotic and a β-lactamase inhibitor, and a surrounding layer around the core, the surrounding layer having a different composition to the core and comprising antibiotic.

Preferred β-lactam antibiotics are β-lactam antibiotics, for example penicillins and cephalosporins, in particular amoxycillin, for example in the form of amoxycillin trihydrate. A preferred β-lactamase inhibitor is clavulanate, particularly potassium clavulanate. In the core the ratio antibiotic : β-lactamase inhibitor may vary between wide limits, in the case of clavulanate for example varying between 1 : 1 to 30 : 1, for example amoxycillin : clavulanate between 1 : 1 to 30 : 1, e.g 2 : 1, 3 : 1, 4 : 1, 5 : 1, 6 : 1, 7 : 1 or 8 : 1 inclusive expressed as the equivalent weight ratios of the parent free acids.

The core may suitably contain a ratio amoxycillin : clavulanate between 1 : 1 to 4 : 1.

The core may be made by a conventional granulating process as known in the art. Preferably the core is made by a dry granulation procedure for example slugging then milling, or by roller compaction then milling. The core may include conventional additives introduced as a result of the granulation process, e.g. lubricants such as magnesium stearate, in conventional quantities, e.g. ca. 1 wt% of magnesium stearate. Suitably the core is a core granule of 10 - 40 mesh size, for example 12 - 30 mesh size.

The surrounding layer may suitably comprise the same antibiotic as is used in the core, for example a β-lactam antibiotic such as amoxycillin trihydrate. The layer may suitably be applied to the core as a mixture of antibiotic with a granulating material, particularly of a type which assists spray granulation, such as cellulose derivatives, e.g. ethylcelluloses, hydroxypropylcelluloses, hydroxypropyl-

methylcelluloses or polyvinylpyrrolidone etc or mixtures thereof. These may be optionally also mixed with a plasticiser material such as propylene glycol, acetyltriethylcitrate, triethyl citrate, dibutyl sebucate, diethylphthalate etc, and dissolved or suspended in a suitable solvent such as water or an organic solvent. The layer may consequently include such materials as well as the antibiotic.

Examples of combinations of granulating material and plasticiser include hydroxypropyl celluloses, hydroxypropylmethyl celluloses and ethyl celluloses, mixed with propylene glycol or acetyltriethylcitrate. Typically the ratio of antibiotic : granulating material : plasticiser in the layer may be in the range 5-10 : 1 - 2 : 1-2 by weight.

By varying such parameters as the quantity of granulating material used or its viscosity or solubility etc the rate of dissolution of the surrounding layer and/or permeability of the layer to water (so allowing dissolution of core materials) may be varied.

In the overall granule the ratio antibiotic : β-lactamase inhibitor may also vary between wide limits, in the case of clavulanate for example varying between 30 : 1 to 1 : 1, for example amoxycillin : clavulanate between 30 : 1 to 1 : 1, e.g 1 : 1, 2 : 1, 3 : 1, 4 : 1, 5 : 1, 6 : 1, 7 : 1 or 8 : 1 expressed as equivalent weight ratios of the parent free acids. Suitably the overall ratio may be in the range around (e.g. ± 10%) 2 : 1 to 4 : 1. Suitably a ratio of around 4 : 1 may be achieved by using a core having a ratio around 3.2 : 1, with a surrounding layer which contains enough amoxycillin to bring the overall ratio up to around 4 : 1. Suitably a ratio of around 2 : 1 may be achieved by using a core having a ratio around 1 : 1, with a surrounding layer which contains enough amoxycillin to bring the overall ratio up to around 2 : 1.

The granule is preferably coated with a coating layer of a dissolution-retarding coating. This coating may be a polymeric material, for example an enteric polymer (the term "enteric polymer" is a term of the art referring to a polymer which is preferentially soluble in the less acid environment of the intestine relative to the more acid environment of the stomach).

An enteric coating may be an essentially conventional coating material known for enteric coating of antibiotic granules, for example enteric polymers such as cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetate phthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, methyl acrylate-methacrylic acid copolymer, methacrylate-methacrylic acid-octyl acrylate copolymer, etc. These may be used either alone or in combination, or together with other polymers than those mentioned above. The enteric coating may also include insoluble substances which are neither decomposed

nor solubilized in living bodies, such as alkyl cellulose derivatives such as ethyl cellulose, crosslinked polymers such as styrene-divinylbenzene copolymer, polysaccharides having hydroxyl groups such as dextran, cellulose derivatives which are treated with bifunctional crosslinking agents such as epichlorohydrin, dichlorohydrin, 1, 2-, 3, 4-diepoxybutane, etc. The enteric coating may also include starch and/or dextrin.

Preferred enteric coating materials are the commercially available "Eudragit" (Trade Mark) enteric polymers, such as "Eudragit L" (Trade Mark), "Eudragit S" (Trade Mark), and "Eudragit NE" (Trade Mark) or mixtures thereof used either alone or with a plasticiser. Such coatings are normally applied using a liquid medium, and the nature of the plasticiser, depends upon whether the medium is aqueous or non-aqueous. Aqueous plasticisers include propylene glycol or "Citroflex" or Citroflex A2" (Trade Marks) (mainly triethyl citrate or acetyl triethyl citrate). Non-aqueous plasticers include these, and also diethyl and dibutyl phthalate, and dibutyl sebacate.

The quantity of plasticiser included will be apparent to those skilled in the art. The enteric coating may also include an anti-tack agent such as talc, silica or glyceryl monostearate. The quantity of plasticiser and anti-tack agent may be generally conventional to the art. Typically the coating may include around 10 - 25 wt.% plasticiser and up to around 50 wt% of anti tack agent, e.g. 5 - 20 wt.% of anti-tack agent.

The enteric coating may be applied to the granules by dissolving or suspending the enteric coating materials in a suitable medium, such as water, methanol, ethanol, isopropanol, acetone, methyl ethyl ketone, methylene dichloride, ethylene chloride, ethyl acetate, etc. or mixtures thereof, and the resultant solution or suspension may be sprayed on the granules to coat them, followed by drying sufficiently with an air flow and screening.

In the case of the preferred enteric coating material referred to above, the enteric coating material may be dissolved or suspended in a solvent for example water and coated onto the granules using a fluidised bed system. If water is used, preferably an anti-foaming agent such as activated polymethylsiloxane is also included. A suitable organic solvent is a propanol-methylene dichloride mixture.

The coating layer may be applied sequentially to the granules, in a batch or continuous process. In a batch process the granules may be removed from the equipment being used to apply the surrounding layer and coated later. In a continuous process, after the surrounding layer had been deposited on the core the nature of the coating solution or suspension may be changed after application of a suitable quantity of the surrounding layer.

The surrounding layer may be pre-treated to apply a hydrophobic material such as a wax, a stearate or a silicone, prior to application of the coating layer, to reduce the rate of water ingress into the granule.

Typically the core may comprise some 30 - 65 wt.%. of the overall granule weight. Suitably the surrounding layer may comprise some 15 - 40 wt. % of the overall granule weight. Suitably the coating layer may comprise 15 - 40 wt. % of the overall granule weight.

The invention therefore also provides a method for the preparation of such a granule, which method comprises forming a core which comprises an antibiotic and a β-lactamase inhibitor, and forming thereon a surrounding layer around the core, the surrounding layer having a different composition to the core and comprising antibiotic, and optionally also coating the granule with a coating layer of a dissolution-retarding coating.

The granules of the invention may be made up into a formulation for oral administration, including appropriate additives and/or pharmaceutically aceptable carriers, in a number of forms.

One form is a compressed tablet formulation comprising granules of the invention dispersed in a matrix which include a β-lactam antibiotic, optionally but preferably together with a β-lactamase inhibitor, which may be the same antibiotic and/or β-lactamase inhibitor which are used in the granule of the invention. A preferred marix antibiotic is amoxycillin, for example amoxycillin trihydrate, and a preferred matrix β-lactamase inhibitor is clavulanate, particularly potassium clavulanate.

In the matrix the ratio antibiotic : β-lactamase inhibitor may vary between wide limits, for example between 1 : 1 to 30 :1, for example amoxycillin: clavulanate between 1:1 to 12:1, e.g. 2:1, 3:1, 4:1, 5:1, 6:1, 7:1 or 8:1 inclusive expressed as the equivalent weight ratios of the parent free acids. Suitably the matrix amoxycillin : clavulanate ratio is between 2:1 and 4:1. Together with the amoxycillin and clavulanate in the granule the overall amoxycillin : clavulanate ratio in the tablet may suitably be in the range 1:1 to 30:1, for example amoxycillin:clavulanate between 1:1 to 12:1, 3:1, 4:1, 5:1, 6:1, 7:1, or 8:1 inclusive expressed as the equivalent weight ratios of the parent free acids. Suitably the overall tablet amoxycillin:clavulanate ratio may be in the range 2:1 to 8:1.

Suitably in such a tablet the relative proportion of amoxycillin in the granules of the invention: matrix amoxycillin may be in the ratio 2:1 to 1:2, typically around 1.5:1 ± 10%, and the relative proportion of clavulanate in the granules of the invention: matrix clavulanate may also be in the ratio 2:1 to 1:2, typically around 1.5:1 ± 10%.

The matrix in such a tablet may also include diluents such as calcium carbonate, magnesium carbonate, dicalcium phosphate or mixtures thereof, binders such as hydroxypropylmethylcellulose, hydroxy-propylcellulose, polyvinyl-pyrrolidone, pre-gelatinised starch or gum acacia or mixtures thereof, disintegrants such as cross-linked polyvinylpyrrolidone, sodium starch glycollate, croscarmellose sodium or mixtures thereof, lubricants, such as magnesium stearate or stearic acid, glidants or flow aids, such as colloidal silica, talc or starch, stabilisers such as desiccating amorphous silica, suspending agents, and compression aids such as microcrystalline cellulose, in conventional amounts. The invention further provides a method for making such a tablet, comprising admixing the granules of the invention and a β-lactam antibiotic, and compressing the mixture into a tablet.

Such a tablet may advantageously produce a sustained release effect, whereby antibiotic and inhibitor are released initially from the matrix, then subsequently or more slowly from the granules. If the granules are coated with an enteric polymer, release may be delayed until the granules pass into the intestine.

Another form is a rapidly-dispersing tablet for swallowing directly, which may comprise compacted granules of this invention. Methods of compacting granules to form a tablet are well known in the art.

Such tablets may be made by any esentially conventional tabletting process, eg compaction of the matrix materials, the granules and any other additives in a tabletting press. During compaction some loss of integrity on crushing of some of the granules may occur, but tablets including such crushed granules are included within the scope of this invention. Such loss of integrity may be reduced by the use of known compaction acids such as starch and microcrystalline celluloses in the matrix.

Another form is a chewable tablet. Appropriate additives comprise a chewable base such as mannitol, microcrystalline cellulose or sorbitol, or mixtures thereof, binders such as polyvinylpyrrolidone (eg Kollidon K12-K30, Trade Mark), an optional disintegrant such as sodium starch glycollate, cross-linked polyvinyl-pyrrolidone, croscarmellose sodium or mixtures thereof, lubricants such as magnesium stearate or stearic acid, glidants or flow aids, such as colloidal silica, talc or starch, and stabilisers such as desiccating amorphous silica.

Such a chewable tablet may alternatively be made up as a fizzy chewable tablet by incorporating into it an effervescent couple, ie a mixture of an acid and a carbonate that evolves carbon dioxide on contact with water. Typical acids include citric and tartaric acid, and typical carbonates include sodium hydrogen carbonate, sodium glycine carbonate and sodium carbonate. By including a disintegrant such as those mentioned above into such a fizzy chewable tablet, a fizzy chewable dispersible tablet may be produced.

Such chewable, fizzy chewable and fizzy chewable dispersible tablets may be made by essentially conventional processes apparent to those skilled in the art.

Another form is an oral suspension, i.e. containing the components in a liquid vehicle for swallowing. Appropriate additives comprise diluents such as methylcellulose, sorbitol, mannitol or starch, or mixtures thereof, suspending agents, such as sodium carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropyl- methylcellulose, gum acacia or mixtures thereof, sweetening agents such as sodium saccharin, sodium cyclamate, acesulfane-K, aspartame or mixtures thereof, preservatives, such as sodium benzoate, sorbic acid, lower alkyl derivatives of p-hydroxybenzoate, flow modifiers such as colloidal silica or amorphous silica, stabilisers, such as desiccating amorphous silica, suspending agents, and colouring and flavouring agents to conventional amounts.

Oral suspensions may be made up from such ingredients into a liquid vehicle in an entirely conventional manner.

Another form is a single dose sachet for make up into an aqueous suspension for swallowing immediately prior to dosing. In this form the chemical nature of the additives may be the same as for the oral suspension described immediately above, typically diluents, sweetening agents, flow modifiers, stabilisers, and colouring and flavouring agents to conventional amounts.

The sachet for such formulations may be entirely conventional but they are advisably substantially airtight to exclude atmospheric moisture.

Another form is swallowable granules, i.e. dry granules for swallowing directly, e.g. washed down with water. Alternatively the granules could be sprinkled onto a meal. Appropriate additives for this form comprise, diluents, such as mannitol, microcrystalline cellulose or sorbitol, or mixtures thereof, binders such as polyvinylpyrrolidone (e.g. Kollidon K12-K30 or VA64, Trade Marks), disintegrants such as sodium starch glycollate, cross-linked polyvinylpyrrolidone or croscarmellose sodium or mixtures thereof, lubricants such as magnesium stearate or stearic acid, glidants or flow aids such as colloidal silica, talc or starch, and stabilisers such as dessicating amporphous silica, sweeteners and flavours to suit local tastes.

The components and additives may be made up into swallowable granules in an essentially conventional manner using for example water, an aqueous solution of a binder, pharmaceutically permitted organic solvents or a solution of a binder in such a solvent.

Another form comprises a capsule formulation in which the first, second, third and optionally fourth components are contained within a water-soluble capsule, e.g. of gelatin.

Another form is a chewable bar. Appropriate additives comprise a bar substrate, such as an oil or cellulose based or other carbohydrate based substance capable of being formed of low temperatures and low moisture content into a bar with suitable organoleptic properties, a sweetener to form the bulk of the bar such as mannitol, and an intense sweetener such as saccharin or aspartame.

If the granules of the invention are to be compacted into a compact form such as a tablet, the coating layer material is preferably selected so as to withstand compaction. Some loss of integrity of the coating material may take place during compaction.

The above-described formulations may comprise solely granules of the invention, in which case such granules may be all essentially identical, or else the granules may differ, for example in their relative antibiotic and/or β-lactamase inhibitor content, the distribution of antibiotic between the core and the surrounding layer, the ratios of antibiotic and β-lactamase inhibitor, the dimensions of the core, surrounding layer and/or the coating, size etc..

Additionally or alternately the formulations may include antibiotic or β-lactamase inhibitor present in particles, e.g. powder and/or granules, other than the above-described granules of this invention and for example having different dissolution characteristics to the granules of the invention. By such variations the ratios of antibiotic : β-lactamase inhibitor in the overall formulation, and/or the rate of release of antibiotic and β-lactamase inhibitor from the formulation after administration may be modified, for example to produce a controlled release formulation.

The above-mentioned formulations for oral administration may contain quantities of antibiotic and β-lactamase inhibitor up to the maximum amount allowed by regulatory authorities. For example in the case of amoxycillin and clavulanate the total amount of amoxycillin may be 875 $\pm$ 100 mg (expressed as the parent free acids), and of clavulanate 250 mg for a daily dose, divided up between one or more unit dosage forms.

Clavulanic acid and its derivatives, e.g. salts such as potassium clavulanate are extremely moisture sensitive, and all operations carried out to prepare granules and formulations of this invention which contain clavulanate should be carried out under conditions of low relative humidity, e.g. less than 30% RH, ideally as low as possible.

The present invention also provides a pharmaceutical formulation as described herein for use as an active therapeutic substance.

The present invention also provides a pharmaceutical formulation as described herein for use in the treatment of bacterial infections.

The present invention also provides the use of a granule or formulation as described herein in the manufacture of a medicament for use in the treatment of bacterial infections.

The present invention also provides a method of treatment of bacterial infections in humans or animals which comprises the administration of an effective amount of a pharmaceutical formulation as described herein.

The invention will now be described by way of non-limiting example only, with reference to Fig 1 which shows a cross section through a granule of the invention, and Fig 2 which shows a cross section through a tablet of the invention.

The granule of Fig 1 consists of a core 1, a surrounding layer 2 and a coating 3.

The tablet of Fig 2 consists of the granules of Fig 1, 4 dispersed within a matrix 5. In Figs 1 and 2 although the granules are shown as spherical, in practice they may have irregular shapes, and the size of the granules 4 is greatly exaggerated relative to the size of the overall tablet.

Example 1.

1. Core	**Components**	**wt. %**
	Amoxycillin trihydrate*	40.0 - 43.0 (as free acid equiv.)
	Potassium clavulanate*	40.0 - 43.0 (as free acid equiv.)
	Magnesium stearate	1.0
2. Surrounding Layer	**Components**	**wt. %**
	Core granules from 1.	62.5
	Amoxycillin trihydrate	25.1 (as free acid equiv.)
	Hydroxypropylmethyl-] -cellulose]	4.1
	Diethyl phthalate	4.1
	Methylene dichloride**	q.s.
	Propan-2-ol**	q.s.
3. Enteric Coating	**Components**	**wt.%**
	Granules from 2	75.0
	Eudragit L30D (TM)	19.5
	Propylene glycol	3.1

Talc	2.0
Antifoam M	0.3
Purified water *	q.s

* Sourced as a 1:1 blend.

** Removed during processing.

Process.

The ingredients for the core granules were dry blended, then dry granulated by slugging and milling. Granules between 12 and 30 mesh were retained for application of the surrounding layer. The core granules were coated with the amoxycillin (dispersed in a solvent system with the binder and plasticiser) in a fluidised bed coater and retained for final enteric coating. The granules were then coated with Eudragit L30D (trade mark), in an aqueous system with additional plasticiser and anti-tack agents, in a fluidised bed coater.

Example 2

1. Core:	**Components**	**wt.%**
	Potassium Clavulanate	24.2
	Amoxycillin Trihydrate	74.8
	Magnesium Stearate	1.0

The components were dry blended then slugged. The slugs are reduced by milling. Granules between 16-30 mesh size are retained as the final product. The granules are stored double wrapped in polythene with dessicant between the layers in a dessicated fibreboard keg.

2. Surrounding layer:	**Components**	**wt.%**
	Core granules from 1	82.22
	Amoxycillin trihydrate BP	14.24
	Propylene glycol BP	1.71
	Hydroxy propylmethyl cellulose Ph. Eur.	1.71
	Antifoam M	0.12
	Purified Water Ph Eur *	q.s.

* removed during processing

Core granules from 1 were coated with an amoxycillin trihydrate coat by co-current spraying in a fluidised bed. The granules are stored in a polythene bag in a dessicated keg.

3. Enteric Coating Layer	Components	wt.%
	Granules from 2	60.00
	Eudragit L30D	33.93
	Eudragit NE30D Ph.Eur	1.79
	Talc, USP/Ph.Eur	3.79
	Antifoam M	0.49
	Purified Water Ph.Eur*	q.s.

* removed during processing.

The granules from 2 were coated with Eudragit by co-current spraying in a fluidised bed.

4. Tabletting	Components	wt. %
	Amoxycillin : Potassium Clavulanate 1:1 blend	6.25
	Amoxycillin Trihydrate	7.50
	Granules from 3	37.50
	Magnesium Stearate	0.50
	Microcrystalline cellulose (Avicel PH 112)	q.s.*
	Calcium Carbonate	q.s.*
	Total compressed mixed weight	100

* These components are present in the ratio 60:40 and a quantity is used sufficient to total 100%.

The components were screened and blended, and compressed to prepare oval tablets 19.0 x 9.0 mm, nominal weight 1000 mg having the structure shown in Fig 2. This formulation provides a 100/150 mg split between quick and delayed release amoxycillin and a 25/37.5 mg split between quick and delayed release clavulanate. The delayed release granules from 3 contain 4:1 amoxycillin:clavulanate.

Example 3

1. Core	Components	wt.%
	Potassium Clavulanate : Amoxycillin trihydrate 1:1 blend)	99.0
	Magnesium stearate	1.0

Procedure as example 2, but 12-30 mesh granules used.

2. Surrounding Layer	Components	wt.%
	Core Granules from 1	62.5
	Amoxycillin trihydrate	28.12
	Diethyl phthalate BP	4.69
	Hydroxypropylmethyl cellulose Ph.Eur.	4.69
	Propan-2-ol BP*	qs
	Methylene dichloride BP*	qs

* removed during processing

Procedure as example 2.

3. Enteric Coating Layer	Components	wt.%
3.1 Non-Aqueous	Granules from 2	70.00
	Eudragit S100, USP	23.68
	Diethyl phthalate BP	3.81
	Talc Ph. Eur.	2.51
	Propan-2-ol BP*	qs
	Methylene dichloride*	qs

* removed during processing

3.2 Aqueous	Granules from 2	60.00
	Eudragit L30D	32.25
	Propylene Glycol Ph.Eur.	5.02
	Talc. Ph. Eur.	3.31
	Antifoam M	0.42
	Purified Water BP*	qs

* removed during processing.

In both the non-aqueous and aqueous cases the granules from 2 were coated with Eudragit by co-current spraying in a fluidised bed.

Claims:

1. A pharmaceutical granule, comprising a core which comprises a β-lactam antibiotic and a β-lactamase inhibitor, and a surrounding layer around the core, the surrounding layer having a different composition to the core and comprising antibiotic.

2. A granule according to claim 1 wherein the antibiotic is amoxycillin, and the β-lactamase inhibitor is clavulanate.

3. A granule according to any one of claims 1 or 2 wherein the surrounding layer comprises amoxycillin.

4. A granule according to any one of the preceding claims coated with a coating layer of a dissolution-retarding coating.

5. A granule according to claim 4 wherein the coating is an enteric polymer.

6. A pharmaceutical formulation for oral administration comprising granules as claimed in any one of claims 1 to 5.

7. A pharmaceutical formulation according to claim 6 being a compressed tablet formulation comprising granules as claimed in any one of claims 1 to 5 dispersed in a matrix which includes a β-lactam antibiotic.

8. A pharmaceutical formulation according to claim 7, wherein the matrix comprises amoxycillin and clavulanate.

9. A method for the preparation of a pharmaceutical granule according to claim 1, which method comprises forming a core which comprises an antibiotic and a β-lactamase inhibitor, and forming thereon a surrounding layer around the core, the surrounding layer having a different composition to the core, and comprising antibiotic, and optionally also coating the granule with a coating layer of a dissolution-retarding coating.

10. A method for the preparation of a pharmaceutical formulation acording to claim 7 comprising admixing said granules with a β-lactam antibiotic and compressing the mixture into a tablet.

11. A pharmaceutical formulation according to any one of claims 1 to 8 for use as an active therapeutic substance.

12. A pharmaceutical formulation according to claims 1 to 8 for use in the treatment of bacterial infections.

13. Use of a granule or formulation according to any one of claims 1 to 8 in the manufacture of a medicament for use in the treatment of bacterial infections.

14. A method of treatment of bacterial infections in humans or animals which comprises the administration of an effective amount of a pharmaceutical formulation according to any one of claims 1 to 8.

Fig. 1

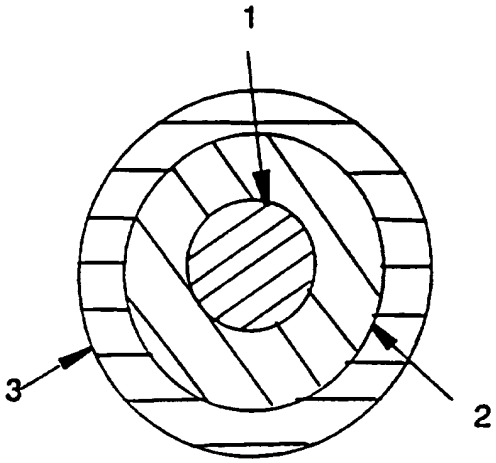
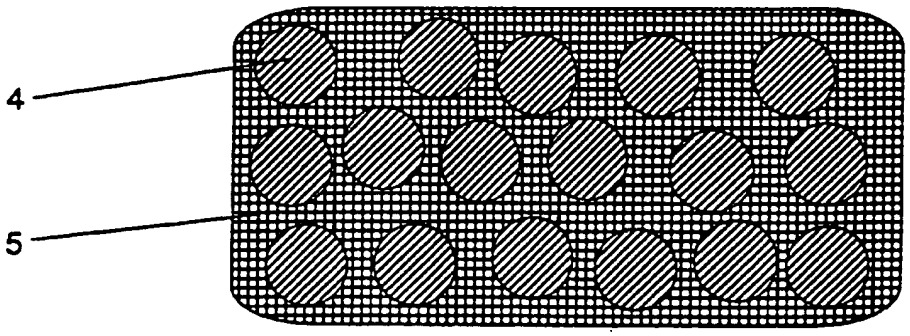


Fig. 2



INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 95/03150

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/43 A61K9/20 A61K9/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 080 862 (BEECHAM GROUP PLC,UK) 8 June 1983 see claims see examples ---	1-3,9, 13,14
A	GB,A,2 005 538 (BEECHAM GROUP LTD.,UK) 25 April 1979 see claims see examples ---	1-3,7,9, 13,14
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
17 November 1995	01.12.95
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Scarponi, U

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INTERNATIONAL SEARCH REPORT

Int ional Application No
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